PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15814-11PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/CA2004/001918	International filing date *(day/month/year)* 03 November 2004 (03-11-2004)	Priority date *(day/month/year)* 03 November 2003 (03-11-2003)

International Patent Classification (IPC) or national classification and IPC
IPC: C07K 7/06 ***(2006.01)*** , C07K 5/04 ***(2006.01)*** , A61K 31/436 ***(2006.01)*** , A61L 31/08 ***(2006.01)*** , A61K 38/04 ***(2006.01)*** , C07K 1/00 ***(2006.01)*** , A61P 37/00 ***(2006.01)*** , A61L 31/16 ***(2006.01)*** , C07D 498/14 ***(2006.01)***

Applicant
ALTACHEM PHARMA LTD. ET AL

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 11 sheets, as follows:
      [X] sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. 1 and the Supplemental Box.
   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - [X] Box No. I Basis of the report
   - [ ] Box No. II Priority
   - [X] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [X] Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI Certain documents cited
   - [ ] Box No. VII Certain defects in the international application
   - [X] Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06 September 2005 (06-09-2005)	7 March 2006 (07-03-2006)
Name and mailing address of the IPEA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Nathalie Chartrand (819) 994-2341

No. I Basis of the report

With regard to the **language**, this report is based on:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into , which is the language of a translation furnished for the purposes of:

- [ ] international search (Rules 12.3(a) and 23.1(b))
- [ ] publication of the international application (Rule 12.4(a))
- [ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

[ ] the international application as originally filed/furnished

[X] the description:

- [X] pages 1-6, 10, 11 and 14 to 47 — as originally filed/furnished
- [X] pages* 7, 8, 12 and 13 — received by this Authority on 3 February 2006
- [X] pages* 9 and 9a — received by this Authority on 6 September 2005

[X] the claims:

- [ ] pages — as originally filed/furnished
- [ ] pages* — as amended (together with any statement) under Article 19
- [X] pages* 48 to 50 and 52 — received by this Authority on 3 February 2006
- [X] pages* 51 — received by this Authority on 6 February 2006

[ ] the drawings:

- [ ] pages — as originally filed/furnished
- [ ] pages* — received by this Authority on
- [ ] pages* — received by this Authority on

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [X] The amendments have resulted in the cancellation of:
   - [X] the description, pages 7 to 9, 12 and 13
   - [X] the claims, Nos. 1 to 18
   - [ ] the drawings, sheets/figs
   - [ ] the sequence listing *(specify):*
   - [ ] any table(s) related to sequence listing *(specify):*

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/figs
   - [ ] the sequence listing *(specify):*
   - [ ] any table(s) related to sequence listing *(specify):*

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

ox No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

he question whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially pplicable have not been examined in respect of:

[ ] the entire international application

[X] claims Nos. 4 to 9, 15 and 16

because:

[X] the said international application, or the said claims Nos. 4 to 9, 15 and 16
relate to the following subject matter which does not require an international preliminary examination *(specify):*

Although claims 4 to 9, 15 and 16 encompass a method of treatment of the human/animal body which this Authority is not required to examine under Rule 67.1 (iv) of the PCT, the preliminary report on patentability has been established on the basis of the alleged effects of the compounds referred to therein.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify):*

[ ] the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed *(specify):*

[ ] no international search report has been established for said claims Nos.

[ ] a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

[ ] furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

[ ] a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	7 to 13	YES
	Claims	1 to 6 and 14 to 18	NO
Inventive step (IS)	Claims	None	YES
	Claims	1 to 18	NO
Industrial applicability (IA)	Claims	1 to 18	YES
	Claims	None	NO

2. Citations and explanations (Rule 70.7)

D1: US 5,411,967 A (AMERICAN HOME PRODUCTS CORPORATION), 2 May, 1995.

D5: WO 03/057218 A1 (NOVARTIS AG), 17 July, 2003.

D6: US 6,585,764 B2 (CORDIS CORPORATION), 1 July, 2003.

Documents D1, D5 and D6 were cited in the first written opinion dated March 14, 2005.

NOVELTY:

Document D1 discloses carbamates of rapamycin which are useful as immunosuppressive, antiinflammatory, antifungal, antiproliferative and antitumor agents. This document discloses rapamycin compounds which are identical to the compound claimed in claims 1 and 2, particularly when the variable R of present claim 1 is an amino alcohol, such as -NH-CH-(R1R2), wherein R1 and R2 are each a hydroxyalkyl or R1 is an alkyl (-CH_3) and R2 is hydroxyalkyl or R1 is hydrogen and R2 is hydroxyalkyl. Also, a compound identical to compound 7o of claim 2 which corresponds to the compound having formula (I) of claim 1 and where R is -NH-CH(R1R2), R1 and R2 are a -CH_2OH is found in D1 columns 2 and 3. Additionally, a process to prepare the compounds is described where 42-O-(4-nitrophenoxycarbonyl) rapamycin and basic conditions are used in the reaction. The compounds, their use in therapy and the process described in the reference D1 fall within the scope of claims 1 to 6 and 14 to 18. A first applicant's response to the written opinion was received on September 6, 2005. In this correspondence, the applicant argues that claims 7 to 13 are novel over D1 because it does not teach rapamycin compounds conjugated to peptides, amino acids or active peptides. Also, the applicant outlines that the rapamycin substituents in D1 are only substituents with no biological effects, which is contrary to the present invention. A second response from the applicant was received on February 3, 2006 to clarify the claims. In this response, it is mentioned that claim 1 has been amended to more definitively claim compounds wherein substituent R is NH-$(A)_n$-CH_2OH or alternative structures as therein defined comprising an amino acid, an amino alcohol or a peptide. Also, the applicant states that by this amendment, the claimed compounds clearly distinguish over the teachings of D1. However, the amendment dated February 3, 2006 does not clarify claim 1 in a way to overcome the teachings of D1. It is true, as mentioned in the first response, that a rapamycin conjugated to a peptide or an amino acid is new and inventive. However, in the case where R is an amino alcohol as defined above, then, new claims 1 and 2 are still encompassed by the teachings of D1. The compounds taught in D1 still encompass the compounds of present claims 1 and 2. Therefore, claims 1 to 6 and 14 to 18 do not comply with Article 33(2) of the PCT in view of D1.

See supplemental sheet

x No. VIII Certain observations on the international application

e following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully pported by the description, are made:

laim 1 is ambiguous and does not comply with Article 6 of the PCT. The definition of the variable R is not clear. It is ecified at the bottom of page 48 that R comprises an amino alcohol. However, the definitions of the variables R1, R2, 4, R5, R6 and R9 are not limited to give an amino alcohol. For example, in the first amino group -NH-CH(R1R2), R1 and 2 are defined as being independently hydrogen, alkyl, hydroxyalkyl or a group CO_2R8. This means that R1 and R2 may ot be a hydroxyalkyl. Finally, the definition of the variable R9 does not correspond to an amino alcohol group, therefore, he amine carrying R9 does not fit the definition of R as an amino alcohol.

Claim 1 is not supported adequately by the description and does not comply with Article 6 of the PCT. The applicant has not provided evidence to show that the conjugation of rapamycin compounds to any combination of 1 to 10 amino acids would be effective in the treatment of cell proliferation diseases. The applicant only shows some effects with rapamycin compounds conjugated with amino acids from the C-terminal of the octapeptide HSKRRLIF. In the applicant's response dated September 6, 2005, it is argued that support is found at the bottom of page 4 and at the beginning of page 5 and that the novelty of the conjugated combinations of 1 to 10 amino acids is believed to be evident. Also, it is mentioned that the octapeptide HSKRRLIF displays potent inhibitory activity towards the CDK2-cyclin complex. The support pointed out by the applicant in the description on pages 4 and 5 is specific for the octapeptide HSKRRLIF. There is no support for a compound comprising any combination of 1 to 10 amino acids. Therefore, a person skilled in the art reading claim 1 would not be able to determine which compound is inhibitory.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

In addition, D1 would fall within the scope of claims 1, 3 to 6 and 14 to 18 if R is -NH-CH-(R1R3) where R1 is H and R3 is a heteroaromatic group. But because it is specified in claim 1 that R comprises an amino alcohol, then R1 would necessarily be a hydroxyalkyl, therefore, the compound corresponding to a rapamycin having an amino heteroaromatic group in the reference D1 would not be identical to the rapamycin compound having a R= -NH-CH-(R1R3) wherein R1 is hydroxyalkyl and R3 is heteroaromatic.

INVENTIVE STEP:

The subject matter of claims 1 to 6 and 14 to 18 is still not novel, therefore, these claims do not define an inventive step under Article 33(3) of the PCT in view of D1.

Document D5 discloses methods to prevent or treat proliferative diseases, especially vascular diseases, by administering a therapeutically effective amount of rapamycin or rapamycin derivatives delivered from any catheter-based device. Also, this document discloses stents coated with rapamycin derivatives.

Document D6 discloses a stent having a coating containing rapamycin and formed from a polymer mixed carrier. This stent is used intravascularly to inhibit restenosis.

It is obvious to a skilled person to use the carbamates of rapamycin described in D1 in a method to prevent or treat proliferative vascular diseases which would comprises the administration of rapamycin compounds described in D1 through any catheter-based devices as described in D5. Therefore, claims 7 to 9 do not define an inventive step under Article 33(3) of the PCT in view of D1 and D5.

Likewise, it is obvious to a skilled person to use a stent as described in D5 or D6 coated with the carbamates of rapamycin described in D1 to inhibit intravascular restenosis. Therefore, claims 10 to 13 do not define an inventive step under Article 33(3) of the PCT in view of documents D1 and D5 or D6.

In applicant's response dated September 6, 2005, it is argued that the molecules in accordance with the present invention are targeted towards the regulation of cdk2, cdk1, cyclin A, D, E, p27, p21 and p70s6 proteins and that the molecules are prepared with a multifunctional purpose which are not described or suggested in the teaching of D1. The applicant states that the claims of the present application are both novel and inventive and thus, patentably distinguish over the teachings of D1 alone or in combination with D5 and D6. However, as discussed above, at page 4 of this report, claims 1 to 6 and 14 to 18 are still lacking novelty in view of D1. Therefore, claims 7 to 9 and 10 to 13 remain obvious to a person skilled in the art in view of D1, D5 and D6.

It is noted however that no prior art compounds having an amino acid or a short peptide of 1 to 10 amino acids linked through a carbamate ester linkage at the 42 position of rapamycin were found. Therefore, the compounds of claim 1 having Formula I, where R is NH-(A)n-CH_2OH, A is D or L amino acid and n is 1 to 10 seem to be novel and inventive.

INDUSTRIAL APPLICABILITY:

Claims 1 to 3, 10 to 14, 17 and 18 appear to define subject matter that has industrial applicability under Article 33(4) of the PCT, based on the function of the compounds of the instant application as inhibitors of cell proliferation disorders.

For the assessment of claims 4 to 9, 15 and 16 on the question of whether or not they define subject matter that has industrial applicability, no unified criteria exists in the PCT. Further, the patentability of said claims can depend upon their formulation. Although the methods *per se* defined in claims 4 to 9, 15 and 16 relate to subject matter which this Authority is not obliged to examine under Rule 67.1 (iv) of the PCT, the use of the compounds referred to therein for treating cell proliferation disorders appears to represent subject matter that has industrial applicability.